Original Article

Impact of Pandemic Influenza (H1N1) Virus-Associated Community-Acquired Pneumonia among Adults in a Tertiary Hospital in Thailand

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(Received March 31, 2010. Accepted May 28, 2010)

SUMMARY: In July 2009, a pandemic influenza (H1N1) (pdm H1N1) virus epidemic emerged rapidly in Phitsanulok, Thailand. Adult cases of community-acquired pneumonia (CAP) were prospectively examined for pdm H1N1 virus infections by real-time PCR in a tertiary hospital in Phitsanulok from July to November 2009. Twenty-four cases of pdm H1N1 virus-associated CAP were confirmed, and their clinical features including bacterial infection, severity of disease, course of admission, treatment, and outcome were investigated. The median age of these cases was 39.5 years. Most cases appeared to be primary viral pneumonia, but only one case was positive for a urinary pneumococcal antigen. The median time from the onset of illness to admission was 4 days. All 24 patients received oseltamivir after admission. Twelve (50.0%) were defined as having severe CAP and 9 (37.5%) were diagnosed with acute respiratory distress syndrome (ARDs). During the study period, pdm H1N1 virus infections frequently caused severe CAP among young adults because of the delayed initiation of antiviral therapy. Of the 9 ARDS patients, 3 died of ventilator-associated pneumonia caused by multidrug-resistant Acinetobacter baumannii. Implementation of infection control targeting this pathogen is required in tertiary hospitals in Thailand.

INTRODUCTION

Since the identification of an outbreak of acute respiratory illness caused by the new swine-origin influenza A (H1N1) virus was identified in Mexico in late March 2009, the virus has rapidly spread throughout the world (1). On June 11, 2009, the World Health Organization (WHO) raised the pandemic alert level to phase 6 suggesting the beginning of a global pandemic (2). Previous observations indicate that most of the infections occurred in children and young adults (3–5). Risk factors for severe disease include chronic lung diseases such as bronchial asthma, immunosuppression, pregnancy, and obesity (4,6–8). Previous studies from Mexico and the United States have reported that a prominent clinical feature of pandemic influenza (H1N1) (pdm H1N1) virus infection is severe community-acquired pneumonia (CAP) among patients between the age of 5 and 59 years (8–10). By the end of July 2009, the geographical distribution of the cases spread to all of the regions of Thailand, including Phitsanulok Province in lower northern Thailand (11,12). In Thailand the most affected age groups were also children and young adults (13). We report herein on the clinical features and outcome of 24 cases of pdm H1N1 virus-associated CAP in adults in a tertiary hospital in Thailand.

MATERIALS AND METHODS

Patients: We prospectively observed adult patients who had been diagnosed as having pdm H1N1-associated CAP and were admitted to a 900-bed tertiary provincial hospital (Buddhachinaraj Hospital) in Phitsanulok, Thailand, between July and November 2009. This hospital treats most of the critically ill
patients including severe CAP, of the entire population (approximately 844,000) of Phitsanulok Province. CAP was defined as a new pulmonary infiltrate found on chest radiographs within 24 h of admission, and where clinical symptoms and signs of pneumonia, such as cough, sputum and fever, were evident (14). Since the epidemic of pdm H1N1 virus infection started in early July in Phitsanulok, all physicians were requested to send throat swab samples from adult CAP patients to the Regional Medical Sciences Center, Phitsanulok, for detection of pdm H1N1 virus using WHO-approved RT-PCR assays (15). During the study period, 24 adult CAP patients with pdm H1N1 virus infection were admitted to the Department of Medicine, Buddhachinaraj Hospital, and these patients were defined as the study subjects. Blood cultures from all 24 patients with pdm H1N1-associated CAP were examined at the time of admission. Sputum cultures of patients were examined where expectorated sputum samples were also available. Fresh nonconcentrated urine samples were also examined using the Binax NOW Streptococcus pneumoniae urinary antigen test (Binax, Portland, Maine, USA), which was processed and interpreted according to information provided by the manufacturer (16).

Data collection: The following parameters of the study subjects were recorded at the time of admission: age, sex, comorbidities, clinical symptoms and signs, chest radiograph findings, microbiological data; and laboratory parameters. Days from the onset of illness to the time of admission, length of hospital stay, ICU admission, receipt of mechanical ventilation, duration of mechanical ventilation, use of antibiotics, antivirals and corticosteroid treatment, and complications of ventilator-associated pneumonia (VAP) were also recorded. The study subjects who met at least 1 of 2 major severe criteria (invasive mechanical ventilator, septic shock with the need for vasoressors) or 3 of 9 minor severe criteria (respiratory rate ≥ 30/min; PaO2/FiO2 < 250; multilobar infiltrates; confusion and/or disorientation; uremia, blood urea nitrogen (BUN) ≥ 20 mg/dL; leucopenia, leukocyte count < 4 × 10^9 cell/L; thrombocytopenia, platelet count < 100 × 10^9/L; hypothermia, core temperature < 36°C; hypotension, systolic blood pressure (SBP) < 90 mmHg) at the time of hospital admission were defined as severe CAP (17). The diagnosis of acute respiratory distress syndrome (ARDS) followed the American-European consensus conference (18). This group defined ARDS as fulfilling the following requirements: (i) PaO2/FiO2 of 200 or less, (ii) a chest radiograph with bilateral pulmonary infiltrates compatible with pulmonary edema; and (iii) no clinical evidence of congestive heart failure. All studies described here were approved by the Ethics Committee and the Institutional Review Board of Buddhachinaraj Hospital.

Statistical analysis: Descriptive statistics of the patients were performed and reported in terms of median and range for the quantitative variables, and in terms of absolute frequencies and percentage for the qualitative variables. Comparisons of the clinical characteristics between the fatal and nonfatal cases were analyzed by using the chi-square test or Fisher’s exact test. Data were considered to be statistically significant, if the P values were less than 0.05.

**RESULTS**

The characteristics of the 24 adult CAP patients with pdm H1N1 virus infection who were admitted between July 8 and October 13, 2009, are shown in Tables 1 and 2. The enrolled study subjects included 6 cases in July, 13 cases in August, 4 cases in September, and one case in October. No infected cases were enrolled in November 2009. The ages of the patients ranged from 18 years to 71 years (median, 39.5 years). Seventy-five percent of the patients were less than 50 years of age. Only two (8.3%) were older than 65 years of age. Of the 24 subjects, 16 (66.7%) had comorbid illnesses. While few patients had upper respiratory symptoms such as a sore throat and rhinorrhea, most patients complained of a cough and the production of sputum. Seven of the 24 patients (29.2%) developed diarrhea. There was notification of the prior use of oral antibiotics before admission in 6 of 24 patients.

At the time of admission, bacterial pathogens were identified from sputum in only two patients (Escherichia coli and Klebsiella pneumoniae in one patient, and Acinetobacter baumannii and K. pneumoniae in another patient). Blood cultures were negative for all of the 24 patients and only one (4.2%) tested positive for the urinary pneumococcal antigen (Table 1). Subsequently, this case (No. 14) had a fatal outcome as shown in Fig. 1. Of the 24 subjects, 8 (33.3%) had mild leukocytosis (median, 13,500 per mm^3) and 2 (8.3%) had

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>no. / total no. (%)</td>
</tr>
<tr>
<td>≥ 18 to &lt; 30 y</td>
<td>4/24 (16.7)</td>
</tr>
<tr>
<td>≥ 30 to &lt; 50 y</td>
<td>14/24 (58.3)</td>
</tr>
<tr>
<td>≥ 50 to &lt; 65 y</td>
<td>4/24 (16.7)</td>
</tr>
<tr>
<td>≥ 65 y</td>
<td>2/24 (8.3)</td>
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<tr>
<td>Symptom</td>
<td></td>
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<tr>
<td>Sore throat</td>
<td>6/24 (25)</td>
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<tr>
<td>Rhinorrhea</td>
<td>5/24 (20.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>20/24 (83.3)</td>
</tr>
<tr>
<td>Sputum</td>
<td>21/24 (87.5)</td>
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<tr>
<td>Hemoptysis</td>
<td>3/24 (12.5)</td>
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<tr>
<td>Dyspnea</td>
<td>16/24 (66.7)</td>
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<tr>
<td>Wheezing</td>
<td>2/24 (8.3)</td>
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<tr>
<td>Diarrhea</td>
<td>7/24 (29.2)</td>
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<td>Comorbid illness</td>
<td></td>
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<tr>
<td>Obesity</td>
<td>5/24 (20.8)</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>4/24 (16.7)</td>
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<tr>
<td>Asthma</td>
<td>2/24 (8.3)</td>
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<tr>
<td>Diabetes</td>
<td>2/24 (8.3)</td>
</tr>
<tr>
<td>Death</td>
<td>5/24 (20.8)</td>
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<tr>
<td>Bacterial examination</td>
<td></td>
</tr>
<tr>
<td>Blood culture</td>
<td>0/24 (0)</td>
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<tr>
<td>Urinary pneumococcal antigen</td>
<td>1/24 (4.2)</td>
</tr>
<tr>
<td>Laboratory finding</td>
<td>median (range)</td>
</tr>
<tr>
<td>Leukocyte count per mm^3</td>
<td>7,165 (2,210–17,800)</td>
</tr>
<tr>
<td>Platelet count × 10^9 per mm^3</td>
<td>225 (62–430)</td>
</tr>
<tr>
<td>BUN mg/dL</td>
<td>16.2 (5–44)</td>
</tr>
<tr>
<td>Creatinine mg/dL</td>
<td>1.0 (0.5–3.7)</td>
</tr>
</tbody>
</table>
leukopenia (2,210 and 2,680 per mm$^3$). Although 6 of the 24 (25%) showed signs of uremia (BUN ≥ 20 mg/dL), an increased level of serum creatinine was found in 2 patients. Radiographic findings of these patients at the time of admission showed multilobular or bilateral infiltrates in 19 patients (79.2%) (Table 2). Twelve (50.0%) were diagnosed with severe CAP. All patients with severe CAP received mechanical ventilation in an ICU, with the exception of case No. 24. This case was admitted to a non-ICU setting. ARDS was diagnosed in 9 patients (37.5%).

Of the 24 patients, 19 were discharged and 5 (20.8%) died. No significant differences were found between the nonfatal and fatal cases with respect to sex, age, days from the onset of illness to admission, or period of admission (Table 2). The median time from the onset of illness to admission was 4 days (range, 2–7 days). None of the patients received antiviral drugs prior to admission. Twenty-two patients received oseltamivir therapy at a dosage of 75 mg twice a day for 5 days and 2 patients (No. 14 and No. 23 in Fig. 1) received combination therapy with oseltamivir at a dosage of 75 mg twice a day and zanamivir at a dosage of 10 mg 2 to 4 times a day for 10 to 14 days immediately after admission. Of the 24 patients, 21 (87.5%) received antibiotics such as ceftriaxone, levofloxacin, or clarithromycin, and 3 patients with non-severe CAP received no antibiotics. While 9 (76.9%) of the 12 patients with severe CAP received corticosteroid treatment (dexamethasone at a dosage of 16 to 24 mg per day), 2 (16.7%) of the 12
patients with non-severe CAP received corticosteroid treatment (dexamethasone at a dosage of 16 mg per day).

Of 9 ARDS cases, 5 (55.6%) survived after mechanical ventilation with positive end-expiratory pressure (Fig. 1). The duration of mechanical ventilation in the 4 fatal ARDS cases (median, 13.5 days; range, 6–38 days) tended to be longer than that for the 5 survivors of the ARDS cases (median, 7 days; range, 5–11 days), although no significant difference was found between the two groups (P = 0.261). A chest radiograph of a patient with ARDS (No. 3), a 30-year-old female without any comorbid illness, showed bilateral interstitial and alveolar infiltrates on the day of admission (Fig. 2A). The period between the onset and admission was 7 days. Although the PaO₂/FiO₂ ratio at admission was as low as 55.0, this patient was successfully treated with mechanical ventilation for 7 days.

Furthermore, 5 survivors received corticosteroid treatment with a median interval of 2 days (range, 1–4 days) from admission. In contrast, of the 4 fatal ARDS cases, only 2 cases received corticosteroid treatment with longer intervals of 4 and 7 days from admission, and the other 2 received no corticosteroid treatment. During the period of treatment for ARDS including corticosteroids, infectious complications frequently occur (19). One ARDS case (No. 5) had hospital-acquired pneumonia (HAP) caused by multi-drug resistant (MDR) A. baumannii following extubation for mechanical ventilation, from which he recovered when treated with antibiotics (Fig. 1). However, the other 3 ARDS cases (Nos. 10, 14, and 23) had VAP caused by MDR A. baumannii and subsequently died. One patient with ARDS (No. 14) was a 45-year-old female with alcoholic liver cirrhosis. The period between the onset and admission was 3 days. Her respiratory condition worsened after admission, as shown by the PaO₂/FiO₂ of 111.1 on the 3rd admission day. After the initiation of mechanical ventilation this patient suffered from VAP caused by MDR A. baumannii on the 7th day after admission, and subsequently developed sepsis and died on the 11th day after admission. A chest radiograph of this case showed bilateral alveolar infiltrates on the 7th day after admission (Fig. 2B). One case of ARDS (No. 16) died of suspected acute myocarditis on the 5th day after admission, and one case of severe CAP with an underlying disease of cerebral palsy (No. 24) died of aspiration pneumonia on the 2nd day after admission. As a result, the occurrence of severe CAP (P = 0.019) or ARDS (P = 0.047) was significantly associated with the observed fatal outcomes (Table 2).

**DISCUSSION**

In the present study, we report on the clinical manifestations and outcome of 24 admitted adult CAP cases with pdm H1N1 virus infection among adults in rural Thailand during July and October 2009. Most of the cases were adults younger than 50 years of age. This finding is consistent with previous reports of pdm H1N1 virus-associated pneumonia from Mexico and the United States (6,8–10), but distinguishable from a recent report of seasonal influenza A pneumonia in Thailand (20). This pdm H1N1 virus more efficiently replicated and caused more severe pathological lesions in the lungs of animals than a seasonal H1N1 influenza virus (21). A recent investigation revealed that influenza A nucleoprotein-positive cells expressed sialic acid (SA) α2-3 galactose (Gal) on the cell surface of type II pneumocytes of an autopsied case of pdm H1N1 infection, suggesting that pdm H1N1 is binding to SAα 2-3 Gal receptors and infecting type II pneumocytes (22). These findings clearly illustrate the nature of pdm H1N1 virus causing primary viral pneumonia.

A recent study reported that oseltamivir therapy is associated with survival in hospitalized patients with influenza pneumonia in Thailand (23), and the median time from the onset of symptoms to the initiation of oseltamivir therapy (4 days; range, 2–7 days) in the 5 fatal cases was longer than those (2 days; range 0–13 days) in the 303 surviving patients. All of our patients received oseltamivir immediately after a median interval of 4 days from the onset of illness to admission. Although no difference was found in the period from
the onset to admission between fatal and nonfatal cases in our study (Table 2), the initiation of antiviral treatment was delayed in most of the patients. Subsequently, 50% and 37.5% of the patients developed severe CAP and ARDS, respectively. With the receipt of mechanical ventilation, 7 patients with severe CAP and 5 patients with ARDS were able to survive. Since this prospective study was conducted in the medical ward of a tertiary hospital, a possible bias in the enrollment of more severe cases cannot be dismissed, and this would be one limitation in this study. Another limitation is that the clinical manifestations of pdm H1N1 virus-associated CAP were investigated only in adults, but not in children, although the most affected groups in Thailand were children and young adults (13).

Although secondary bacterial pneumonia was a common cause of death during the 1918 influenza pandemic (24), the series of recent studies dealing with pdm H1N1 virus infections demonstrated that the common causes of death were viral pneumonia and ARDS, and bacterial coinfections were found in only a few cases (6,9,10,25). Only one indicative case of pneumococcal pneumonia using urinary antigen test was confirmed in 24 adult CAP patients with pdm H1N1 virus infection in our study, although a possible influence of prior antibiotic use before admission cannot be dismissed. In contrast, in a recent postmortem study of fatal cases of confirmed pdm H1N1 virus infections in the United States, evidence of bacterial coinfections was found in 22 (29%) of 77 patients, including 10 cases caused by *S. pneumoniae* (26). Furthermore, a recent study of 199 patients with pdm H1N1 virus infection from Argentina reported an association of *S. pneumoniae* with severe disease defined as death or requiring hospitalization, although bacterial DNA was detected only in the nasopharyngeal swab samples from patients by PCR in this study (27). Another recent study from Argentina reported 9% of 325 adult patients with confirmed, probable, or suspectd pdm H1N1 infection with acute respiratory failure had pneumonia caused by *S. pneumoniae* (28). Concomitant pneumococcal pneumonia was an independent predictor of hospital mortality in this study. Collectively, bacterial coinfections appear to be less common among patients with pdm H1N1 virus-associated pneumonia including our 24 patients, but if present such co-infections may cause severe disease or fatal outcomes.

In our study, 3 of the 5 fatal cases were complicated with VAP caused by MDR *A. baumannii*. Despite extensive antimicrobial treatments including colistin (29), these patients subsequently developed sepsis and died. A recent study of National Antimicrobial Resistance Surveillance reported an increasing trend of MDR or carbapanem-resistant *A. baumannii* in Thailand (30). Chaladchalam et al. reported 22 cases of VAP caused by MRD *A. baumannii* in a hospital in Bangkok, Thailand (31). The authors found an environmental contamination of this pathogen in bed rails and endotracheal tubes in most of these patients. Of note, a high incidence of VAP caused by *A. baumannii* and *Pseudomonas aeruginosa* was also reported in adult patients of pdm H1N1 infection with acute respiratory failure, requiring mechanical ventilator in Argentina (28). Therefore, a complication of VAP caused by such nosocomial pathogens is a critical problem for adult patients of pdm H1N1 infection with severe CAP or ARDS during hospital admission worldwide.

Although the role of corticosteroids in the treatment of ARDS in adults is inconclusive at present (32), a recent study reported that the early administration of methylprednisolone inhibits systemic inflammation, and improves acute lung injury and reduces the duration of mechanical ventilation among severe ARDS patients (33). Therefore, researchers from Argentina have recently proposed a combination therapy involving oseltamivir and prolonged methylprednisolone administration for patients with pdm H1N1 virus-associated ARDS (34). Most of our patients with ARDS received dexamethasone in combination with antivirals because of its low cost. However, the use of dexamethasone may increase the risk of infectious complications such as VAP (18,35). Further studies are required for the appropriate use of corticosteroids in combination with antiviral agents for pdm H1N1 virus-associated ARDS.

In conclusion, most of the 24 admitted patients with pdm H1N1 virus-associated CAP were young adults. Twelve patients had severe CAP and the 9 were diagnosed as ARDS because of the delayed initiation of antiviral therapy. Of the 9 ARDS patients, 3 died of VAP caused by MDR *A. baumannii*. Therefore, the infection control targeting this pathogen should be strengthened for management of pdm H1N1 virus-associated ARDS in tertiary hospitals in Thailand.

Acknowledgments The authors wish to thank Dr. Prasert Khungern and the staff of Department of Medicine and Infection Control Team, Buddhachinaraj Hospital, for their support of this study.

This study was supported in part by the Department of Medical Sciences, Ministry of Public Health, Thailand, the Program of Research Centers for Emerging and Reemerging Infectious Diseases launched by a project commissioned by the Ministry of Education, Culture, Sports, Science and Technology of Japan, and Grants-in-Aid from the Ministry of Health, Labour and Welfare of Japan on “Mechanisms, epidemiology, prevention and control of acute respiratory infection.”

Conflict of interest None to declare.

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through suppressing iNOS gene expression and peroxygenit